Rocky Mountain Spotted Fever Presenting as Febrile Pancytopenia

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After this patient's laboratory work and examination, a diagnosis still eluded physicians. Only after further questioning and a final test did they conclude a diagnosis of Rocky Mountain spotted fever.

A 20-year-old soldier presented to the emergency room with a 1-day history of nausea, vomiting, diarrhea, and fever of 102°F. He had recently arrived in San Antonio after extended training at Fort Leonard Wood, Missouri. He denied abdominal pain, melena, or any sick contacts.

ASSESSMENT

He was afebrile at the time of admission with a heart rate of 78 beats per minute, blood pressure 111/63 mm Hg, respiratory rate 18 breaths per minute, and oxygen saturation 99% of room air. No abnormalities were noted on the physical examination, including skin rashes or lesions. His initial admission laboratory work values were all within normal limits.

Although the patient was initially thought to have viral gastroenteritis, he continued to have intermittent fevers as high as 103.2°F. His hospital course was complicated by the following peculiar laboratory abnormalities: His white blood cell count dropped to 1.8 x 10^3 cells/mm^3 with an absolute neutrophil count of 0.41 x 10^3 cells/mm^3, a hematocrit of 33.2%, and a platelet count of 58,000 platelets/mm^3. His international normalized ratio (INR) was 1.3, alanine transaminase rose to 620 U/L, aspartate transaminase 544 U/L, and he had a lactate dehydrogenase (LDH) of 310 U/L. A direct antibody test was negative for hemolysis. His hepatitis and cytomegalovirus (CMV) serologies were negative. His HIV test came back negative as well. Radiographic studies included a right upper quadrant ultrasound that showed no evidence of intrahepatic or extrahepatic biliary dilatation, normal echogenicity of the liver without lesions, and a normal gallbladder. Due to his neutropenia and his continued fevers, he was placed on neutropenic precautions and started on broad-spectrum antibiotics. A bone marrow biopsy to further investigate his pancytopenia was unremarkable.

Daily and frequent questioning of his risk factors and history finally led to his possible diagnosis. During his last week of training at Fort Leonard Wood, he remembered pulling off a tick that seemed firmly lodged into his skin. Rickettsial titers were drawn and revealed an IgG titer of 1:64 and IgM titer of 1:64, suggesting the diagnosis of Rocky Mountain spotted fever (RMSF).

DIAGNOSIS

The differential diagnosis for nausea, vomiting, and diarrhea is vast. However, when gastroenterocolitis is coupled with fevers, pancytopenias, and transaminitis, the differential diagnosis becomes more concise. Even with this spectrum of findings, RMSF would still not be high on many physician's differential diagnosis list. A careful history and frequent questioning finally helped us diagnose this mystery.

RMSF is a tick-borne bacterial illness caused by *Rickettsia rickettsii*, a small obligate, intracellular, gram-negative coccobacillus.[1] As an obligate intracellular organism, RMSF typically infects endothelial cells of the small vessels of all major organ systems. This mode of infection can lead to a diverse range of symptoms due to damage that can occur to the skin, brain, lungs, heart, gastrointestinal tract, kidneys, and skeletal muscles.[2] Endemic to the Western Hemisphere, cases have been reported in Canada, Mexico, Panama, Costa Rica, Argentina, Brazil, and Colombia.[1] However, RMSF continues to be the most lethal tick-borne disease in the United States with risk factors for fatality that include age > 60 years, > 5-day interval between disease onset and treatment,

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lack of tetracycline treatment, or chloramphenicol-only treatment.[1,2]

In the United States, RMSF is typically transmitted by the American dog tick (*Dermacentor variabilis*) in the eastern and central states and by the wood tick (*Dermacentor andersoni*) in the western states. Recently though, a third vector was found to have caused the disease in Arizona, the brown dog tick (*Rhipicephalus sanguineus*).[3] Normally, this vector is found in Mexico and Colombia, whereas the Cayenne tick (*Amblyomma cajennense*) is the typical vector for the other Latin American countries.[1,4] In the United States, most cases occur between April and September with the highest incidence occurring in May and June; however, cases have been reported in every month of the year with most of the fall-winter cases occurring in southern states.[2]

Diagnosing RMSF can be difficult due to the nonspecific symptoms it can cause. A history of a tick bite within the previous 2 weeks is helpful; however, according to case series, approximately 60% of cases report a known tick bite.[5] RMSF has a mean incubation period of 7 days with a range of 2 to 14 days before clinical symptoms become present. The classical clinical triad of rash, fever, and headache is seen in only 60% to 70% of patients, and as much as 9% to 12% of cases do not have a rash at all during the course of the disease. Typically, a small erythematous macular rash first appears on the wrists and ankles within the first 2 to 5 days after fevers begin and then spreads to the palms and soles before progressing to the arms, legs, and trunk. During its progression, the rash often changes from macular to maculopapular with central petechiae.[1,5] Fevers can be high, often above 102°F, and other nonspecific symptoms, such as malaise, headache, myalgias, nausea, vomiting, diarrhea, and abdominal pain predominate early in the disease course. Such symptoms often lead to a misdiagnosis, such as an acute viral illness.[1,2,5]

However, unlike a simple viral illness, RMSF can have other, more specific symptoms and more serious effects on its host. Relative bradycardia, bilateral periorbital edema, conjunctival suffusion, calf tenderness, and edema of the dorsal aspect of the hands or feet have been described with this disease.[6] Pneumonia, cough, hepatomegaly, acute renal failure, hemolysis, neurological manifestations, and ophthamological manifestations have all been known to complicate the course of the disease.[1,7] Laboratory findings can include leukopenia, thrombocytopenia, anemia, elevated aminotransferases, hyperbilirubinemia, and increased creatine kinase levels.[2,8]

Diagnosis is further hindered by a lack of a timely confirmatory laboratory test. Serological testing in the short-term is unhelpful because antibodies to *Rickettsia rickettsii* are not detectable for about 7 to 10 days after the disease onset.[8] Hence, the diagnosis and determination to initiate treatment relies on the history and physical exam. The gold standard for serological testing is the indirect fluorescent antibody test, which detects the surface proteins OmpA and OmpB; typically a 4-fold rise in titers or a titer greater than 1:64 is considered to be diagnostic.[1] For those patients who develop a rash, a direct immunofluorescence test or immunoperoxidase staining of skin biopsy can be used for diagnosis. Regard-

less of the testing performed, a low clinical suspicion for RMSF should be enough to initiate antibiotic therapy without having the test results available for confirmation.

MANAGEMENT

RMSF is adequately treated with any of the tetracyclines; however, because of its effectiveness, dosing schedule, and safety, doxycycline remains the drug of choice for almost all patients. The recommended dose is 100 mg twice a day for adults, and it should be given for a minimum of 5 to 7 days and for at least 2 or 3 days after the patient defervesces. Again, therapy should be initiated on clinical suspicion before confirmatory testing is completed. In pregnant women, doxycyline is contraindicated, so the recommended therapy is chloramphenicol. It should be given as 50 to 75 mg/kg per day divided into 4 doses for the same duration of therapy as doxycycline.[1,2] For those patients who receive timely antibiotic therapy and survive the initial onset of the illness, complete resolution of the disease is expected. Usually no long-term sequelae exist after recovery from the illness, but there have been reports of a few patients who had peripheral neuropathy, hemiparesis, or deafness associated with severe disease.[7]

Our patient was started on doxycycline 100 mg per dose twice a day with gradual resolution of his symptoms and his laboratory values. He was discharged and appropriate follow-up was arranged. His case highlights the common error in diagnosis often seen in patients with RMSF mistaken for an acute viral illness. ●

Author disclosures

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